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Association between body mass index and insulin resistance in survivors of pediatric acute lymphoblastic leukemia

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Original Article**Association between body mass index and insulin resistance in survivors of pediatric acute lymphoblastic leukemia****Running head:** pediatric acute lymphoblastic leukemiaGholamreza Bahoush ¹, Porya Salajegheh ², Farzaneh Rohani ^{3,4*}

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Abstract

In this retrospective cohort study, oral glucose tolerance testing (OGTT) was performed for all enrolled survivors of patients who suffered from acute lymphoblastic leukemia (ALL) at least 9 months after ending chemotherapy, as well as for control group. All demographic, treatment and anthropomorphic data were obtained from medical records. Furthermore, insulin resistance was evaluated according to insulin level, Matsuda and HOMA-IR index. Of 53 subjects, 28 exhibited B-cell ALL, and 25 were healthy children (F/M = 1.12/1). Mean age (\pm SD) was determined to be 10.77 ± 2.83 years, and meantime off for therapy was also recorded as 3.0 ± 1.6 years. ALL patients were diagnosed at age 1–15 years; none of them received the cranial radiotherapy, and demographic characteristics (age, sex, and sexual maturity) were found to be the same in both groups. Seven patients showed transient hyperglycemia during ALL treatment, however, no significant differences were found in terms of body mass index (BMI) means between ALL patients with and without transient hyperglycemia. Based on the data presented herein, insulin resistance could not be predicted by glucose levels during therapy, cumulative asparaginase, and steroid. Our findings demonstrated that elevated BMI could be a valuable predictor of insulin resistance probability in ALL patients. The presence of transient hyperglycemia does not appear to be associated with the increased risk of glucose intolerance or insulin resistance in the first few years after completion of therapy.

Keywords: Body Mass Index, Insulin Resistance, Pediatric Acute Lymphoblastic Leukemia.

Introduction

Advances in the treatment of children with ALL have led to marked improvements in survival, where there is an expanding list of chemotherapy drugs. Increasing the survival of these children has raised new concerns, especially about the long-term side effects of these drugs. Many studies have emphasized the incidence of these complications, especially in the elderly such as obesity and abnormal weight ¹. Furthermore, disturbances in blood lipid profile, hyperglycemia, and insulin resistance are other known complications ². These abnormalities can lead to deadly cardiovascular disease and type 2 diabetes in these patients ³. Despite the high prevalence of these complications and the poor prognosis of these abnormalities, studies in this field have not yet been able to specifically identify the major risk factors for hormonal imbalances ⁴.

Studies have shown that two of the important drugs used to treat these patients are corticosteroids and asparaginase. Hyperglycemia is a common complication for both drug groups, most commonly in the induction phase of treatment, because both drugs are used concurrently. It was found to be capable of developing transient hyperglycemia and could be most frequently occurred in patients with obesity, Down syndrome, a family history of diabetes, and over 10 years of age ⁵. Contrary to the severity of the complication, transient hyperglycemia improves without compromising the patient. Although many studies confirm that those treated usually have high FBS and insulin resistance, they could not prove metabolic complications following transient hyperglycemia. The efficacy of different therapeutic approaches and different doses of medication on the incidence of these complications have not been well understood in previous studies. Therefore, prognostic markers may be capable of preventing the full onset of the complication ⁶.

On the other hand, the treatment of complications such as diabetes is not completely possible and its symptoms lead to high costs and wasted manpower. Therefore, interest has focused markedly on the prevention aspects and identification of prognostic markers is of great importance in preventing these complications. BMI is a more important indicator in this regard ⁷. BMI calculation is a simple, inexpensive and affordable index. Nevertheless, if this index is powerful, it may be used as an appropriate, available, and mandatory index in predicting the hormonal complications of chemotherapy, and all subsequent follow-up of these patients^{8,9}. As a result, it is likely to be capable of preventing the severity of secondary hormonal complications such as diabetes, obesity by subsequent preventive therapies ¹⁰.

On the other hand, the components of the BMI index, height, and weight, are also affected by repeated chemotherapy. Some studies reported lower stature growth in these children as compared to normal children ¹¹ and others pointed to excessive weight gain in them. These components (i.e., height in childhood and weight even at an older age) are highly modifiable, therefore, the imbalance in this index can be reduced by modifying the above risk factors for cardiovascular complications and diabetes ^{12,13}.

Materials and methods

This retrospective (historical) cohort was conducted in Ali-Asghar Medical Center, Tehran, Iran. Children treated for ALL with complete medical records were enrolled in the study who had elapsed after their treatment for at least 9 months and were referred for follow-up care. Convenience sampling was considered based on the medical records of patients admitted to the hospital with ALL.

Inclusion criteria included 1- Age at diagnosis between 0 and 15 years, 2- Having informed consent, 3. Diagnosis of lymphoblastic leukemia. Exclusion criteria included 1- Incomplete medical records (> 20% of all information), 2. Children with relapsed or metastatic disease. Since the principle of this scheme calculates the correlation between the two quantitative amounts of BMI and insulin resistance, the lowest r calculated in the study was 0.03. According to the formula, if the first type error by 5% with a study power of 80%, the number of samples can be calculated as follows

- $(Z_a - Z_b/C) + 3 = n$
- $C = 0.5 * \ln(1 + 0.3/1 - 0.3)$, $N = 62$

The initial sample size is assumed to be at most 60 (50 to 60) to prevent potential plan problems and to avoid decreasing study power due to difficulties.

In the first step, patients' data were extracted from their medical records, including date of diagnosis, age at diagnosis, highest blood glucose obtained during treatment, cumulative doses of corticosteroid and asparagine, type of disease (B-cell or T-cell).

These two criteria (height and weight at diagnosis) are used to calculate the patient's BMI at diagnosis. According to the Centers for Disease Control and Prevention (CDC) criteria, a BMI greater than or equal to 85% is considered a risk factor for overweight and a BMI greater than 95% for age is considered overweight. In the second step, medical records of children as those listed above were extracted and followed upped after treatment. Informed consent was obtained from patients' parents. All patients were fasted for at least 12 hours, then their blood glucose,

fasting insulin and HbA1C values were measured. Their blood samples were taken 0, 60, and 120 minutes after taking 1.75 mg/kg of oral glucose solution. Based on these samples, glucose metabolism was calculated and insulin-resistant disease was diagnosed based on the fasting insulin of >115 mU/m or a maximum blood insulin level of >150 mU/ml. To further investigate insulin resistance, the HOMA and Matsuda criteria were also calculated for patients. The HOMA index is based on insulin resistance of >4 in adolescents and children and >2.5 in adults (HOMA-IR was calculated according to the formula: fasting insulin (microU/L) \times fasting glucose (nmol/L)/22.5). Matsuda index was determined for expressing rd values (Rate of Disappearance of Plasma Glucose) by the glucose clamp technique. The Matsuda index was calculated according to the formula: $10000 / \sqrt{(FPI \times FPG) \times (xGPC \times xIPC)}$; Where FPI is fasting plasma insulin expressed as uU/ml, FPG is fasting plasma glucose expressed as mg/dL, xGPC is mean plasma glucose concentration after the load and xIPC is the mean insulin concentration after the load). According to published results, patients without insulin resistance have a Matsuda index of ≥ 3 .

FBS ≥ 126 mg/dL was considered for diabetes or blood glucose of 200 two hours after glucose consumption. FBS levels of 100–125 mg/dl; or blood glucose of >140 two hours post-consumption of glucose.

All data were analyzed by SPSS 17 software using Pearson correlation. P-value <0.05 was considered significant.

Results

Of the 53 patients, 28 were ALL patients and 25 healthy controls. All patients showed B-cell disease and none of the patients had CRT. Type of regimen was the same in all patients and cumulative doses of corticosteroid and asparagine were determined on the same basis.

Demographic characteristics of the two groups

In the present study, the mean age of ALL patients and the control group were determined as 10.45 ± 3.041 years and 11.13 ± 2.587 years, respectively. The mean age of the patients was 10.77 ± 2.83 years. According to the t-test results, there was no significant difference between the ALL and control groups in terms of age (Chi-Square Tests = 0.976 and $P = 0.323$). The frequency of puberty status is summarized in Table 3. The majority of immature individuals belonged to ALL patients (14%, 50%), followed by the control group (11%; 44%). Based on the results presented in Table 1, no significant difference was found between the two groups in terms of maturity status (Chi-Square Tests = 1.487 and $P = 0.475$).

Table 1: Frequency of puberty status in ALL and control groups

		ALL		Control group	
		Frequency	Percentage in group	Frequency	Percentage in group
puberty status	Immature	14	50	11	44
	Middle Maturity	6	21.4	9	36
	Mature	8	28.6	5	20

The mean cumulative doses of corticosteroid and asparagine in all patients with ALL are presented in Table 2. An average dose of 53742.86 mg /m² was determined for asparagine and 1065.7 mg /m² for corticosteroids.

Table 2: Mean cumulative doses of corticosteroid and asparagine in ALL patients

	Mean (mg/m ²)	Number	Minimum	Maximum	SD
asparagine	53742.86	28	35200	96800	15584.309
Corticosteroid	1065.70	28	698	1920	309.030

The mean weight was also recorded as 36.11 ± 14.114 kg and 42.76 ± 11.281 kg for ALL and control groups, respectively. Furthermore, the mean height was found to be 136.86 ± 16.46 cm in the ALL group and 143.52 ± 11.276 cm in the control group. There was no significant difference in weight and height between the ALL and healthy groups (Weight: T test = - 1.880 and P = 0.066), (Height: T test = - 1.698 and P = 0.096). The mean BMI in the ALL and healthy groups was also calculated as 18.8 ± 2.805 and 20.49 ± 3.952, respectively. The mean BMI of all patients was calculated to be 19.6 ± 3.467 (minimum = 13.3 and maximum = 28). However, no significant difference was observed between the two groups in terms of BMI (T = - 1.816 and P = 0.075).

The mean BMI SDS of patients was evaluated in Table 3. BMI SDS was used to remove the effect of age and sex on BMI and values above 1.28 were considered obese. Overall, the mean BMI SDS of the patients was determined 0.63 ± 0.879 (minimum = - 0.94 and maximum = 2.66), which is presented in Table 3 along with the standard deviation in the ALL and control groups.

Based on the findings presented herein, no significant difference was seen between the two groups in terms of SDS BMI (T = - 0.874 and P = 0.386).

Table 3: Mean BMI SDS in ALL and control groups

	Mean BMI SDS	Number	Minimum	Maximum	SD
ALL	0.53	28	-0.94	2.66	0.834
Normal	0.74	25	-0.90	2.15	0.930

The Frequency of BMI staging status was evaluated in the present study. Our findings showed that lower BMI was seen in 15 (53.6%) out of 53 ALL patients, followed by normal range (12 patients, 42.9%) and out of normal range (3.6%, 1 subject). In the control group, 8 (32%) showed lower BMI, followed by normal range (14 patients, 56%) and out of normal range (3 patients, 12%). No significant difference was found between the ALL and control groups regarding BMI staging status (Chi-Square Tests = 3.124, P = 0.210).

Table 4 shows the frequency of insulin resistance status. The frequency of insulin resistance status based on insulin levels, Matsuda index and HOMA index are indicated in Table 4. No significant difference was found between the two groups in terms of insulin resistance based on insulin levels, Matsuda and HOMA indices.

Table 4: Frequency of insulin resistance based on blood sugar levels

		ALL		Control		Chi-square	
		Frequency	Percentage in group	Frequency	Percentage in group	χ^2	P-value
insulin resistance	Insulin levels	9	32.1	8	32	0.000	0.991
	Matsuda Index	3	10.7	3	12	0.022	0.883
	HOMA index	6	21.4	5	20	0.016	0.585

Correlation of BMI increase with Matsuda and HOMA criteria was evaluated in the ALL treated group (Table 5). There was a significant relationship between insulin resistance and its absence in terms of Matsuda index, HOMA, and BMI in ALL treated patients, where the kappa coefficient was positive for all three indices.

Table 5: Relationship between BMI increase and Matsuda and HOMA indices

BMI increase			Yes	No	Chi-square		Risk estimate			Kappa
			no (%)	no (%)	χ^2	P-value	value	95% CI		
								lower	upper	
insulin resistance	Matsuda Index	yes	3 (25)	9 (75)	4.480	0.034	2.778	1.647	4.685	117.2
		no	0	16 (100)						
	HOMA index	yes	6 (100)	6 (27.3)	10.182	0.001	3.667	1.853	7.255	191.3
		no	0	16 (72.7)						
	Total	yes	6 (100)	6 (27.3)	10.182	0.001	3.667	1.853	7.255	191.3
		no	0	16 (72.7)						

Table 6 compares BMI with Matsuda and Homa criteria in the healthy group, where no significant relationship was found between insulin resistance and its absence according to Matsuda index, HOMA, and BMI in the healthy group. Kappa coefficient was found to be negative for all three indices.

Table 6: Relationship of BMI increase with Matsuda and HOMA indices

BMI increase			Yes		No		Chi-square		Kappa
			Frequency	Percentage in group	Frequency	Percentage in group	χ^2	P-value	
insulin resistance	Matsuda Index	Yes	0	0	8	36.4	1/604	0.205	-1.267
		No	3	100	14	63.6			
	HOMA index	Yes	0	0	8	40	2/941	0.086	-1.715
		No	5	100	12	60			
	Total	Yes	3	25	5	38.5	0/502	0.471	-0.721
		No	9	75	8	61.5			

The relationship between transient hyperglycemia in ALL treated patients was investigated during treatment and insulin resistance (Table 7). The frequency of insulin resistance status based on insulin levels, Matsuda index and HOMA index among 28 treated ALL patients without hyperglycemia during treatment are presented in Table 7. No significant difference was revealed between the two groups with and without transient hyperglycemia in terms of insulin resistance status.

Table 7: Frequency of insulin resistance based on blood sugar levels

		Hyperglycemic		No hyperglycemia		Chi-square	
		Frequency	Percentage in group	Frequency	Percentage in group	χ^2	P-value
insulin resistance based on	Insulin level	0	0	0	0	-	-
	Matsuda Index	0	0	3	14.3	1.120	0.290
	Index HOMA	1	14.3	5	23.8	0.283	0.595

Correlation between BMI increases after treatment of ALL patients with insulin resistance was calculated based on Matsuda criteria. Of the 28 ALL patients, 3 insulin resistance patients (100%) exhibited high BMI, and 9 (36%) showed high BMI.

However, 16 (64%) insulin resistance patients showed low BMI. Our findings revealed a significant difference between the two groups (with and without BMI) in terms of Matsuda criteria (Chi-Square Tests = 4.480 and $P = 0.034$). According to the HOMA criterion, 6 (100%) out of 28 ALL patients with insulin resistance exhibited high BMI and 6 patients without insulin resistance (27.3%) had high BMI. The remaining 16 (72.7%) patients without insulin resistance revealed no BMI elevation. There was a significant difference between the two groups (with and without BMI) in terms of insulin resistance based on Homa criteria (Chi-Square Tests = 10.182 and $P = 0.001$).

The association between post-treatment BMI in ALL treated patients with total insulin resistance (based on insulin level, Matsuda's and HOMA criteria) was calculated. The results revealed that 6 (100%) patients with increased BMI had insulin resistance and 6 patients without insulin resistance exhibited increased BMI. Furthermore, 16 patients (72.7%) without increased BMI did not show insulin resistance. A significant difference was found between the two groups (with and without BMI) in terms of total insulin resistance (based on insulin level, Matsuda criteria, and HOMA) (Chi-Square Tests = 10.182 and $P = 0.001$). The association between BMI elevations over one year in healthy subjects with insulin resistance was calculated based on Matsuda criteria (Table 8). No significant difference between the two groups (with and without BMI) in terms of insulin resistance according to the Matsuda criterion (Chi-Square Tests = 1.604 and $P = 0.205$).

Table 8: Frequency of BMI elevation over one year in healthy subjects based on Matsuda criteria

		Insulin resistance based on Matsuda criteria			
		Yes		No	
		Frequency	Percentage in group	Frequency	Percentage in group
BMI increase	Yes	0	0	8	36.4
	No	3	100	14	63.6

Correlation between BMI elevations over one year in healthy subjects with insulin resistance was calculated on the basis of HOMA criteria (Table 9).

There was no significant difference between the two groups (with and without BMI) in terms of insulin resistance according to HOMA criteria (Chi-Square Tests = 2.941 and P-value = 0.086).

Table 9: Frequency of BMI increase over one year in healthy individuals based on HOMA criteria

		Insulin resistance based on HOMA criteria			
		Yes		No	
		Frequency	Percentage in group	Frequency	Percentage in group
BMI increase	Yes	0	0	8	40
	No	5	100	12	60

The association between BMI over one year was calculated for healthy subjects with total insulin resistance (based on insulin levels, Matsuda's and HOMA criteria) (Table 10). However, no significant difference was observed between the two groups with and without increased BMI in terms of total insulin resistance (based on insulin level, Matsuda's and HOMA criteria), (Chi-Square Tests = 0.520 and P = 0.471).

Table 10: Frequency of BMI elevation over one year in healthy subjects in terms of total insulin resistance

		Total insulin resistance			
		Yes		No	
		Frequency	Percentage in group	Frequency	Percentage in group
BMI increase	Yes	3	25	5	38.5
	No	9	75	8	61.5

Discussion

ALL is one of the most common childhood malignancies which are accounted for 25% of childhood malignancies and 75% of childhood leukemia¹⁴. Improved therapeutic strategies increase the chances of treatment for these children, but the long-term side effects of chemotherapy have raised concerns regarding insulin resistance and obesity. Insulin resistance is one of the key features of metabolic syndrome and an early defect in the development of type 2 diabetes¹⁵. Reports also indicated the role of insulin resistance in the development of the cardiovascular disease. Therefore, we assessed the relationship between the BMI index and insulin resistance in children treated for leukemia.

Fifty-three subjects including 28 ALL and 25 healthy individuals were enrolled in the study. Patients with ALL showed B-cell disease and none of them had CRT. The treatment regimen was the same in all patients and cumulative doses of corticosteroid and asparagine were determined according to the protocol. No significant difference was found in demographic characteristics between the two groups. In the current study, insulin resistance was evaluated based on three criteria including insulin level, Matsuda and HOMA criteria. The association between BMI and insulin resistance was evaluated on the basis of each criterion by considering the incidence of resistance based on one of the criteria, in two groups. A significant relationship was seen between BMI elevation and insulin resistance in ALL treated patients according to Matsuda and HOMA criteria, but not in healthy subjects. This may prove that increased BMI can be a valuable predictor for insulin resistance probability during the treatment of ALL patients. Therefore, proper diet, management of drug complication and modification of treatment protocols in such people can be helpful. In 2009, Dr. Roberson and colleagues evaluated 871 treated children, where 141 children developed transient hyperglycemia during treatment in the US. The rate of treatment, overall survival, recurrence in the groups with and without this complication did not differ, therefore, this team does not consider this effect as a hindrance to current doses of chemotherapy by investigating the short-term side effects of pediatric treatment¹¹.

In our study, there was no association between transient hyperglycemia in terms of insulin resistance among ALL treated patients.

Correlation of BMI increase with Matsuda and HOMA criteria in both ALL treated and healthy groups were evaluated by the chi-square test and Kappa coefficient. Kappa coefficient was found to be positive in ALL treated groups, while this statistic was negative for the healthy groups. Another study by Chorob and colleagues reported two cases of complication among treated patients who both needed hospitalization and insulin use early. They reported a significant relationship between the incidences of this complication with the use of asparaginase¹⁶. Dr. Wang and his colleagues have reported cases of secondary diabetes caused by corticosteroid therapy among their patients, all of whom have been forced to start insulin therapy. Polyuria and hyperglycemia during treatment have been reported in these patients, consistent with our study¹⁷.

In another study by Lowas et al, nearly 42% of all treated people showed transient hyperglycemia, where diabetes and obesity were indicated as the most important secondary and long-term side effects. They also found a clear relationship between the use of asparaginase and the incidence of this complication. However, this research group did not find a clear link between the use of medications and the development of stable diabetes in their subsequent research.

Conclusion

The findings revealed that BMI could be a favorable predictor of insulin resistance probability in ALL patients. The presence of transient hyperglycemia does not appear to be associated with the increased risk of glucose intolerance or insulin resistance in the first few years after completion of therapy.

Conflict of interest

None

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